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| 10/816,099 | 03/31/2004 | Katalin Varadi | P-279.00 | 9454 |

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| EXAMINER | |
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| KOSSON, ROSANNE | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Applicants assert that the claimed invention is not obvious, because none of the cited references discloses a lyophilized substrate comprising calcium chloride and a fluorescently labeled thrombin substrate. In reply, the rejection is one of obviousness, not anticipation. As previously discussed, Váradi et al. disclose the claimed thrombin substrate for a thrombin generation assay that contains a fluorescent label, the polypeptide Z-Gly-Gly-Arg-AMC. Váradi et al. also disclose an aqueous assay reagent comprising 1 mM thrombin substrate and 15 mM calcium chloride (see p. 2375, Thrombin generation assay). This reference does not disclose how this reagent was made. But the advantages of lyophilized reagents for kits and clinical assays were recognized at the time of the invention and are disclosed by Hawkins et al. (see col. 1, line 36, to col. 2, line 7). Lyophilized reagents have minimal variability from lot to lot. Also, one of ordinary skill in the art would have known that lyophilization reduces weight and volume for shipping purposes and imparts stability and shelf-life to reagents, factors which are important for kits. Applicants assert that the fluorescent substrate of Váradi et al. is dried and not lyophilized, but there is no indication of this feature in the reference.

Applicants assert that the claimed invention is not obvious, because the feature that a lyophilized mixture of the polypeptide Z-Gly-Gly-Arg-AMC and calcium chloride, when hydrated to produce an aqueous solution of 1 mM polypeptide and 15 mM calcium chloride, produces a clear solution is a surprising result. Applicants note that the amount of DMSO in the lyophilized mixture does not matter. In reply, as previously discussed, this result is not surprising, because, as noted above, Váradi et al. make this solution and conduct clinical assays with it. They report no problems with cloudiness, precipitation, instability or undesired side reactions. Thus, this argument is not persuasive of non-obviousness. Applicants have not explained how, before the time of the invention, clinicians and scientists in Applicants' field felt or had evidence that lyophilization damaged the fluorescently labeled polypeptide.

Regarding Applicants' Declaration under 37 CFR 1.132, filed to remove Váradi et al. as prior art, Applicants assert that they disagree with Examiner's comment that the Declaration contains a statement that Inventors Keil and Peyrer-Heimstaett did not contribute to the subject matter of the reference. In reply, Part 3 of the Declaration states that these two inventors are not authors because their contribution to the instantly claimed invention is not disclosed in the article by Váradi et al. In light of this sentence, these two inventors do not appear to have contributed to the work of Váradi et al., and Applicants have not explained how these two inventors could or should have been authors.

Applicants assert that they are not required to provide any evidence that these two inventors could have been authors, because authorship and inventorship are different. Applicants assert that the purpose of the Declaration is to attest that the instant inventors invented the claimed subject matter. Applicants assert that Váradi et al. are not relevant to the claims and that whether or not the two inventors named above are authors is not relevant.

In reply, the inventorship in the instant application is not in question. The rejection is one of obviousness, not incorrect inventorship (i.e., the rejection is not one under §102(f)). The relationship of Váradi et al. to the instant claims has been discussed multiple times. That is, Váradi et al. et al. disclose an aqueous solution comprising 1 mM Z-Gly-Gly-Arg-AMC and 15 mM calcium chloride, and the lyophilization of this solution to form a reagent for a clinical assay kit is an obvious modification.

As for providing evidence that the two inventors could have been authors, this point was in the context that there are three possibilities for antedating a reference. This evidence is needed for the third possibility. As previously discussed, first, the inventorship may be changed to match the authors of the reference. Inventors Keil and Peyrer-Heimstaett may be deleted, along with a Katz Declaration disclaiming the authors of Váradi et al. who are not inventors as

not having contributed intellectually to the paper. Alternatively, second, the reference may be antedated with supporting evidence in a Declaration under 37 CFR §1.131. Or, third, Applicants may show, with concrete supporting evidence (such as notebook pages or notes and slides from meetings), that inventors who are not authors could have been authors, i.e., that they contributed intellectually and substantively to the subject matter published in the reference. They provided certain key ideas and explained how the studies to test or prove these ideas should be carried out. But, because of the statement in the Declaration that Inventors Keil and Peyrer-Heimstaett did not contribute to the subject matter of the reference, this third option is not available. The point that these two inventors are not authors is very relevant. Nevertheless, Applicants have two other options.

Because the reference is still prior art, a holding of obviousness is again required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Tues., Wed., Fri., 8:30-6:00, Mon., 8:30-2:00, Thurs. off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
2010-03-26

/Karen Cochrane Carlson/
Primary Examiner, Art Unit 1656